N-Alkylation of Pyrazolones with OH-Protection

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The synthesis of a biheterocyclic compound containing two pyrazolone sub-units, precursor of a new macrocyclic family, is described. It is shown that it is necessary to protect first the pyrazol-5-one oxygen site before condensing it with a bifunctional compound in order to obtain a selective alkylation on the heterocyclic nitrogen atom.

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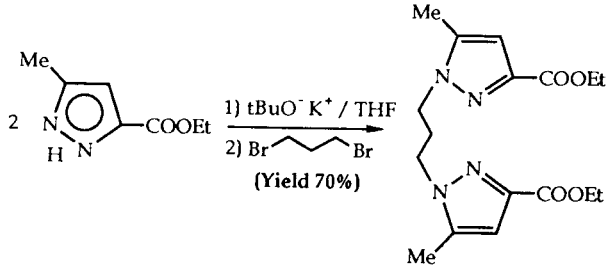
Introduction.

The condensation of 3(5)-carbethoxy-5(3)-methylpyrazole with 1,3-dibromopropane is a well known reaction used as starting for macrocyclic synthesis [1] (see Scheme 1). Our purpose was to use this same method from the 3(5)-carbethoxypyrazol-5(3)one.

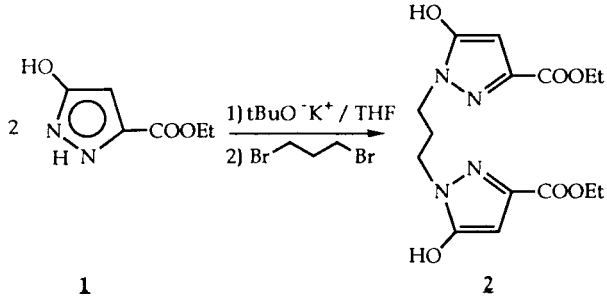
Scheme 1



Results and Discussion.

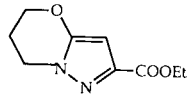
The operative conditions we first used were exactly the same as those reported for the pyrazole derivative, as shown in Scheme 2.

Scheme 2



1 **2**

Under these conditions, the product isolated is the biheterocycle **3**, which results from a double attack of the pyrazolone on the dibrominated derivative.

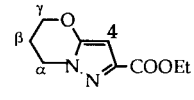


3

The nmr characteristics of compound **3** are presented in Table 1.

Table 1

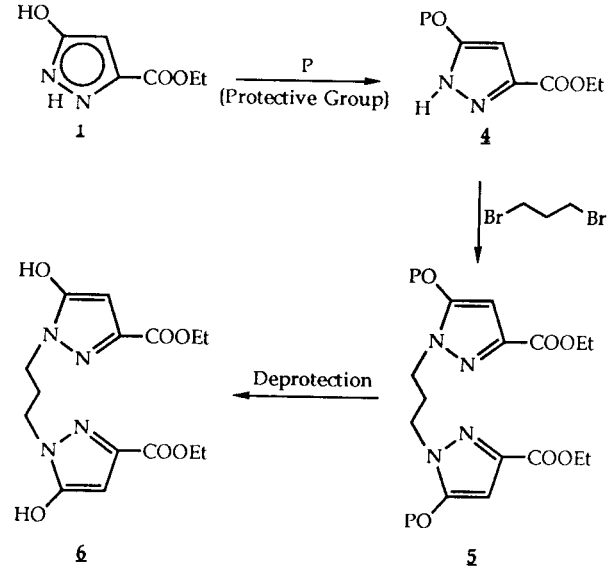
^{1}H NMR data of compound **3** in $CDCl_3$



	H-4	Hα	Hβ	Hγ	CH_3(COOEt)	CH_2(COOEt)
δ(ppm)	6.00	4.24	4.26	2.29	1,36	1.36
	s, 2H	m, 2H	t, 2H	t, 2H	m, 2H	q, 4H

The formation of such a product may originate from the presence in the starting pyrazolone **1** of the OH and NH groups having very close reactivities; potassium *tertio*-butylate may generate both O^- and N^- anions making the intramolecular cyclisation more favorable than the intermolecular condensation, leading to compound **3**.

Scheme 3



After several unsuccessful attemps to modify nature of the solvent and the base (sodium hydride/THF, potassium hydroxide/methanol, sodium hydroxide/DMF), it seemed to us that it was necessary to protect the pyrazolone. The modified process is described in Scheme 3.

To our knowledge, no method leading to *O*-protected pyrazol-3(5)-ones under mild conditions has been described. Protection of the OH function as a methyl ether is not conceivable, this group being too difficult to cleave afterwards.

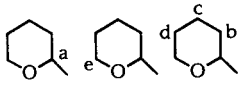
The choice of a protective group is made difficult both because of the experimental conditions used in the alkylation reaction and because of the presence of other functional groups within the molecule. We had to satisfy three requirements: (1) the protective group must be stable under basic medium; (2) the protecting and deprotecting conditions must be mild in order not to disturb the ester function; and (3) the protection must be selective for an OH group. Numerous protective groups for alcohols and phenols have been reported in the literature [2] but generally they also block the amine functions. We chose as the protective group the dihydropyran function which seems to satisfy all the requirements; such a group has been used both for alcohols [3] and for phenols [4] and the reaction occurs preferentially on the alcohol function rather than on the amine one [5].

After optimizing the experimental conditions, we isolated two compounds: the first one **4a** is preferentially formed in tetrahydrofuran; the second one **4b** is obtained in acetonitrile. A study by mass spectrometry shows that **4a** and **4b** have the same molecular weights, identical fragmentations and that they correspond to protected compounds.

The ^{1}H nmr data are presented in Table 2. The spectra obtained for compounds **4a** and **4b** are very close except for the chemical shifts of the pyrazolone ring proton and for the proton *a* of the protecting group. Comparison of the ir spectra of **4a** and **4b** with that of the 3(5)-carbethoxypyrazol-5(3)-one, shows that the C=O stretching band at 1719 cm^{-1} is broadened for compound **4b** (the more polar protected product).

Table 2

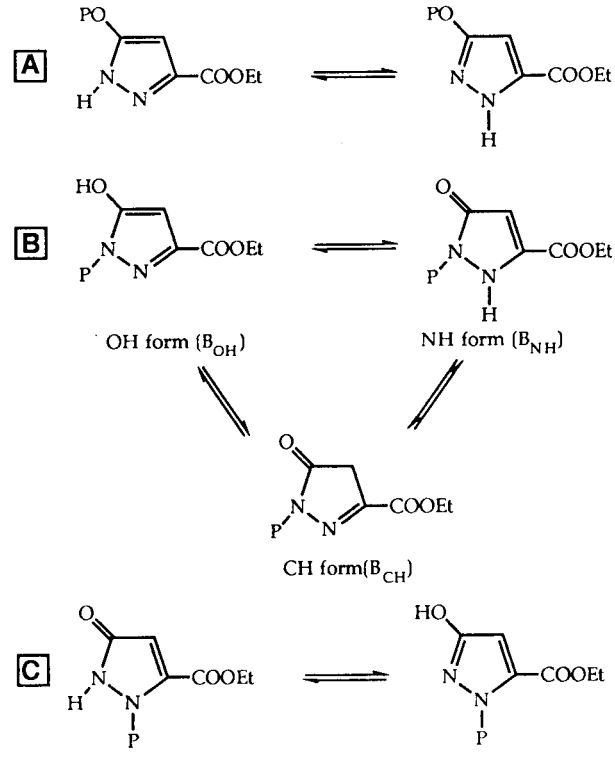
^{1}H NMR data for the 3(5)-carbethoxypyrazol-5(3)one **1** and compounds **4a** and **4b** in $CDCl_3$

δ(ppm)	H-4	CH_2 (COOEt)	CH_3 (COOEt)		
1	6.20, s	4.43, q			
4a	6.24, s	4.33, q	1.35, t	6.18, dd	4.10, bd group 3.69, bt 1.50-2.30
4b	5.98, s	4.30, q	1.31, t	5.50, dd	4.08, bd group 3.65, bt 1.47-2.40

Three structures **A, B, C**, each in equilibrium with tautomeric forms may correspond to all the physico-chemical data found for compounds **4a** and **4b** (see Scheme 4).

In order to decide on the right structures, we undertook a ^{13}C nmr study, the method of choice to obtain significant indications on the molecular skeleton itself. The results are given in Table 3.

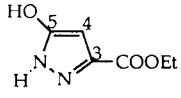
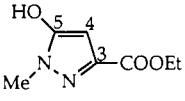
Scheme 4



The nature of the more polar compound **4b** has been unambiguously identified from a comparison with the 3-carbethoxy-1-methylpyrazol-5-one ^{13}C nmr spectrum: both compounds give very similar chemical shifts for the heterocyclic carbon atoms. This observation leads to the conclusion for a structure similar to that corresponding to form **B**; the $\mathbf{B}_{CH}$ form may be ruled out as we did not observe any ^{1}H nmr signal corresponding to a CH_2 signal. As far as the other protected compound **4a** is concerned, we had then to choose between structures **A** and **C**; the formation of the last one is unlikely because the nucleophilicity of the nitrogen atom α to the ester group must be greatly reduced. Furthermore the ir spectrum of compound **4a** does not show any broadening of the ν CO band which could occur in structure **C**. Thus, compound **4a** must have structure **A**, resulting from an *O*-protection. This structure is confirmed because bipyrazole **5** is obtained when **4a** is condensed with the 1,3-dibromopropane in THF in the presence of potassium *tertio*butylate.

Table 3

^{13}C NMR data of the 3-carbethoxypyrazol-5-one, 3-carbethoxy-1-methylpyrazol-5-one and of compounds **4a** et **4b** in $CDCl_3$

δ(ppm)	C_3	C_4	C_5	C=O (COOEt)	CH_2 (COOEt)	CH_3 (COOEt)	a	e	b	d	c
	134.7	93.3	161.8	168.8	62.7	14.5	----	----	----	----	
4a	134.1	97.9	159.7	161.6	61.7	14.5	85.1	69.0	30.4	25.4	23,6
4b	142.8	90.5	154.0	162.9	61.6	14.5	83.7	68.8	29.8	25.1	23,1
	141.3	89.9	154.0	162.9	61.6	14.5	N-CH_3 : 34.1				

In the following steps necessary to reach the macrocycle, we will use the protected bipyrazole **5**; but we preferred to verify first on a small amount how the cleavage of the tetrahydropyranyl ether was occurring in such structures. The deprotecting reaction carried out under mild conditions (room temperature, with a catalytic amount of PPTS), has been followed by ^1H nmr spectroscopy, using deuterated chloroform as the solvent. We rapidly observed the loss of the protective group and a shift to low field (about +0.1 ppm) of the signal corresponding to the heterocyclic proton, showing the formation of the deprotected bipyrazol-5-one **6**.

EXPERIMENTAL

The ^1H and ^{13}C nmr spectra have been recorded on a Bruker AC 250 spectrometer; chemical shifts are given in ppm using TMS as the internal reference. Mass spectra have been obtained with a JEOL JMX DX-333 apparatus. The ir spectra have been recorded on a Philips PU 9700 apparatus. Melting points are uncorrected.

The 3(5)-carbethoxypyrazol-5(3)-one and the 3-carbethoxy-1-methylpyrazol-5-one have been prepared as reported earlier [6].

3(5)-Carbethoxypyrazol-5(3)-one **1**.

This compound was obtained in 78% yield, mp 170°; ms: m/z 156; ^1H nmr: see Table 2.

3-Carbethoxy-1-methylpyrazol-5-one.

This compound was obtained in 75% yield, mp 150°; ms: m/z 170; ^1H nmr (deuteriochloroform): δ 5.95 (s, H-4), 4.31 (q, -O-CH_2-CH_3), 3.71 (s, N-CH_3), 1.30 (t, -O-CH_2-CH_3).

Protection of the 3(5)-carbethoxypyrazol-5(3)one **1**.

The reaction has been carried out following the method described by Miyashita *et al.* [3] for alcohols. Pyrazolone **1** (0.1 mole), dihydropyrane (0.4 mole) and a catalytic amount of pyridinium *para*-toluenesulfonate were mixed at room temperature; when the reaction was carried out in tetrahydrofuran, the less polar *O*-protected **4a** was isolated after about 24 hours (the reaction was monitored by tlc). The solvent was removed *in vacuo* and the oil was purified on a silica gel column (eluent: dichloromethane/ethanol 95/5), yield 40%, mp 128°; ms: m/z 240.

Anal. Calcd. for $C_{11}H_{16}N_2O_4$: C, 55.00; H, 6.66; N, 11.66. Found: C, 55.34; H, 6.49; N, 11.52.

When acetonitrile was used as the solvent, the more polar *N*-protected compound **4b** was obtained. After 24 hours, the solution was evaporated to dryness leading to an oil purified by chromatography on silica gel (eluent: dichloromethane/ethyl acetate 50/50), yield 70%, mp 140°; ms: m/z 240.

Anal. Calcd. for $C_{11}H_{16}N_2O_4$: C, 55.00; H, 6.66; N, 11.66. Found: C, 55.25; H, 6.46; N, 11.49.

The ^1H and ^{13}C nmr data corresponding to compounds **4a** and **4b** are given in Tables 2 and 3.

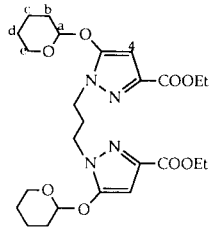
Condensation of 1,3-Dibromopropane with pyrazolones **1** and **4a**.

A mixture of pyrazolone ester (50 mmoles) and potassium *tertio*butylate (50 mmoles) in anhydrous THF (50 ml) was refluxed for one hour. After the addition of dibromopropane (25 mmole), the solution was refluxed for 12 hours, filtered on celite and concentrated and the residue was chromatographed.

Compound **2** was purified on an alumina column eluted with a mixture (dichloromethane/ethyl acetate 70/30), yield 23%; ms: m/z 196; ^1H nmr: see Table 1; ^{13}C nmr (deuteriochloroform): δ 142.1 (C-3), 89.2 (C-4), 151.9 (C-5), 162.6 (C=O), 61.0 (CH_2(COOEt)), 14.6 (CH_3(COOEt)), 45.2 (NCH_2), 22.0 (-CH_2-), 66.0 (OCH_2).

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.10; H, 6.12; N, 14.28. Found: C, 55.35; H, 5.97; N, 14.46.

Compound **5** was purified on a silica gel column eluted with a mixture (dichloromethane/ethyl acetate 96/4), yield 15%, mp 207°; ms: m/z 520; nmr data for:



^{1}H nmr (deuteriochloroform): δ 6.26 (s, 2H, H-4), 4.30 (m, 4H, $NCH_2CH_2CH_2N$), 2.20 (m, 2H, $NCH_2CH_2CH_2N$), 4.30 (m, 4H, OCH_2CH_3), 1.38 (t, 6H, OCH_2CH_3), 6.16 (dd, 2H, H-a), 1.60-2.55 (m, 12H, H-b, H-c, H-d), 4.05 and 3.70 (bd and bt, 4H, H-e); ^{13}C nmr (deuteriochloroform): δ 133.7 (C-3), 97.4 (C-4), 159.7 (C-5), 162.1 (C=O), 61.5 (CH_2(COOEt)), 14.6 (CH_3(COOEt)), 66.3 (NCH_2), 29.5 (-CH_2-), 84.9 (C-a), 29.7 (C-b), 23.3 (C-c), 25.4 (C-d), 68.4 (C-e).

Anal. Calcd. for $C_{25}H_{36}N_4O_8$: C, 57.69; H, 6.92; N, 10.76. Found: C, 57.93; H, 7.21; N, 10.89.

REFERENCES AND NOTES

* Author to whom correspondence should be addressed.

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